Remarks

Status of the Claims and Support for the Amendments

By the foregoing amendments, claims 1-2, 21, 27-31, 59, 60, 77-80, 82-86, 102-104 and 106-108 are sought to be amended, and new claim 109 is sought to be added. Claim 22 has been canceled without prejudice or disclaimer. Support for the amendments to the claims, and for new claim 109, can be found throughout the Specification. For example, support for the amendments to claims 30 and 85 can be found at page 28, paragraph 73, line 14. Support for the amendments to claims 1-2, and 60 can be found at page 22, paragraph 62; at page 57, paragraph 141 and in claim 22 as originally filed. The amendments to claims 28-31, 77-80, 82-86, 102, and 106 are sought to correct inadvertent typographical errors. Support for new claim 109 can be found in claim 21 as originally filed. Therefore, these amendments introduce no new matter, and their entry and consideration are respectfully requested.

Upon entry of the foregoing amendments, claims 1-21, 23-38, 59-96, and 101-109 are pending in the application, with claims 1 and 59 being the independent claims. Claims 12, 16, 28-29, 31-34, 36-37, 68, 72, 83-84, 86-89, 91 and 92 have been withdrawn from consideration by the Examiner.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

Summary of the Office Action

In the Office Action dated August 22, 2007, the Examiner has made four rejections of the claims. The Examiner also acknowledged Applicants' election of Group

I, with the species of GM-CSF, and dihydroxy-poly(ethylene glycol). To further prosecution, the search was extended to a PEGylated species of TNF with PEG-α,β-bis-vinyl-sulfone.

Rejections under 35 U.S.C. § 112 Second Paragraph

In the Office Action at page 2, the Examiner has rejected claims 1-11, 13-15, 17-27, 30, 35 and 38 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

The Examiner contends that it is unclear how more than one bioactive component can be present in the conjugate when the claims recite that the PEG is attached to a single bioactive component. Applicants respectfully traverse this rejection.

Present claim 1 (and hence, claims 2-11, 13-15, 17-27, 30, 35 and 38 which ultimately depend therefrom) recites a conjugate comprising one or more bioactive components covalently attached to at least one linear or branched polyalkylene glycol, wherein each said polyalkylene glycol is attached to one of said bioactive components at a single site on the polyalkylene glycol and said polyalkylene glycol, if linear, has a hydroxyl group at a distal terminus and, if branched, has a hydroxyl group at every distal terminus.

Applicants respectfully submit that present claim 1 recites that each polyalkylene glycol is attached to one of the bioactive components. This language is consistent with the preamble which recites a conjugate comprising one or more bioactive components, and hence, is not indefinite.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejections under 35 U.S.C. § 112 First Paragraph, Written Description

In the Office Action at pages 3-6, the Examiner has rejected claims 1-11, 13-15, 17-27, 30, 35, 38, 59-67, 69-71, 73-82, 85, 90, 93-96, and 101-108 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Examiner states that:

> the claims are drawn to conjugates comprising one or more bioactive component[s] covalently attached to a linear or branched polyalkylene glycol. The base claim does not define the bioactive agent and subsequent dependent claims 27-31, while claiming specific biological agents, also claims mimic [sic] or functional agonist[s] of any of the specific peptides/proteins claimed. The generic statement of [a] biologically active agent or mimic of [sic] functional antagonist, does not provide ample written description for the compounds since the claims do not describe a single structural feature.

Office Action at page 4, last two lines, through page 5, line 5. The Examiner therefore concludes that the specification fails to provide adequate written description for the genus recited in the claims. Applicants respectfully disagree with the Examiner's contentions and conclusions.

As referenced by the Examiner, the MPEP lists several factors that can be used to determine if sufficient evidence of possession of an invention has been furnished in the

disclosure of an application. One such factor is the "level of skill and knowledge in the art." Office Action at page 3, last paragraph. In addition, as the Federal Circuit has held, the written description requirement must be viewed in light of the state of the art at the time of filing. *Capon v. Eshhar,* 418 F.3d 1349, 1357-1358 (Fed Cir. 2005) ("[t]he descriptive text needed to meet these [written description] requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence.").

Applicants respectfully submit that, at the time of filing of the present application, the level of skill and knowledge in the art of PEGylation technology was very high. The ordinarily skilled artisan would have readily understood, based on the present specification viewed in the context of knowledge available at the time of filing of the present application, that any and all peptide/non-peptide bioactive agents, as well as muteins, mimetics, antagonists, variants, analogs and derivatives thereof, could be utilized in the practice of the presently claimed invention.

Specifically, the present specification discloses several exemplary polyalkylene oxide-conjugated bioactive agents. These include, methoxy-PEG adenosine deaminase, methoxy-PEG superoxide dismutase, methoxy-PEG-urate oxidase, and methoxy-PEG GM-CSF. Such non-limiting examples can be found in the specification at page 3, paragraph 6, and at page 5, paragraph 9. The disclosure of multiple exemplary representative species of methoxy-PEG conjugated bioactive agents in the present specification, in combination with the high level of skill in the art, would have allowed the ordinary skilled artisan to envision the full scope of the presently claimed invention. Importantly, whether the bioactive agent is an agonist, antagonist, mimetic, naturally

occurring protein, mutant protein, or protein analog, has no bearing on the ability of one or ordinary skill in the art to readily recognize that such compounds could be conjugated to the hydroxy-polyalkylene glycol molecules (e.g., hydroxy-PEG or "PharmaPEG®") disclosed in the present specification. Furthermore, as the Examiner has noted in the Office Action, page 5, lines 5-17, the present specification discloses at pages 27-29, paragraphs 72-75, and 77, numerous examples of bioactive agents that can be used in the practice of the presently claimed invention.

Other factors in the MPEP cited by the Examiner useful for determining whether a specification has met the Written Description requirement include partial structure, physical structure and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Applicants respectfully submit that these requirements have been met in the present specification, as the structures, chemical properties, and functional characteristics of the recited protein/non-protein bioactive agents were all well known at the time of filing, in the same way as the DNA sequences used to make the chimeric genes were known in *Capon. Id* at 1358. Regarding the method of making the presently claimed invention, Applicants respectfully submit that one of ordinary skill in the art of PEGylation technology, instructed by the disclosure of the present specification, would have been able to readily synthesize any number of hydroxy-polyalkylene glycolated compounds using well-known biochemical procedures (*see* discussion below regarding the rejection under 35 U.S.C. § 112, first paragraph, enablement). Therefore, the present specification clearly possesses all of the factors set forth in the MPEP and identified by the Examiner.

The Examiner also states that:

> the specific peptide/non-peptide bioactive agents do not provide written description for all of the bioactive agents, mimetic[s], and functional antagonist[s] of the claimed invention.

Office Action, page 5, line 19. The Examiner has also cited *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), for the proposition that the specification must provide a representative number of species to identify a claimed genus. Office Action, page 4, line 3-5. Applicants respectfully submit that *Capon* clarifies the written description requirement as delineated by *Fiers v. Revel*, 984 F.2d 1164, 1169 (Fed. Cir. 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991) and *Eli Lilly,* 119 F.3d at 1559. In discussing the current state of the written description requirement under 35 U.S.C. §112, first paragraph, the Federal Circuit stated "[s]ince the law is applied to each invention *in view of the state of relevant knowledge*, its application will vary with differences in the state of knowledge in the field . . . ." *Capon*, 418 F.3d at 1357-1358 (emphasis added). In reviewing and reversing the Board's decision, the Federal Circuit held that "[t]he Board erred in refusing to consider the state of scientific knowledge . . . ." *Id.* Furthermore, the Federal Circuit stated that the Board's reliance on *Eli Lilly, Fiers, Amgen v. Chugai* and *Enzo Biochem Inc., v. GenProbe, Inc.,* 296 F.3d 1316 (Fed. Cir. 2002) for the case at bar was incorrect and explained that "[n]one of the cases to which the Board attributes the requirement of total DNA re-analysis, *i.e.*, *Regents v. Lilly, Fiers v. Revel, Amgen* [*v. Chugai*], *or Enzo Biochem*, require a re-description of what was already known." *Id.*

Furthermore, the Federal Circuit stated:

> The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the *same way*. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution. Both Eshhar and Capon explain that this invention does not concern the discovery of gene function or structure, as in *Lilly*. The chimeric genes here at issue are prepared from *known* DNA sequences of *known* function. The Board's requirement that these sequence must be analyzed and reported in the specification *does not add descriptive substance*.

Id. at 1358 (emphasis added). As in *Capon*, the presently claimed invention does not concern the discovery of any particular bioactive agent, mimetic or functional agonist. Rather, the presently claimed invention is concerned with the modification of *known* bioactive agents in such a manner as to enhance therapeutic efficacy (*e.g.,* reduced antigenicity, elevated stability, etc.). The peptide/non-peptide bioactive agents utilized in the presently claimed invention, including muteins, variants, analogs, mimetics, agonists and derivatives of these agents, represent well-known agents with well known structures and functions. Describing every agent, mutein, variant, mimetic, agonist, analog or derivative that could be used in the practice of the presently claimed invention would not add descriptive substance to the present application, and hence is not required under *Capon*. *Id.*

The Examiner is reminded that Applicants are not required to describe an entire family of bioactive agents that are already well known in the art. Rather, as held in *Capon*, when the art includes the relevant information, "precedent does not set a *per se* rule that the information must be determined afresh." *Capon,* 418 F.3d at 1358. In this light, Applicants are not required to disclose every bioactive peptide/non-peptide agent,

nor every mutein, variant, mimetic, agonist, analog or derivative, that is useful in the present claims, since the art has previously recognized and reported the structures and functions of such bioactive agents, as well as methods for determining whether or not such muteins, variants, mimetics, agonists, etc., possess a particular biological activity of the native or wild-type protein. *See also*, *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1073 (Fed. Cir. 2005), holding that description of a single species is sufficient written description for claims directed to a modified polypeptide having DNA polymerase activity. Therefore, Applicants submit, in view of the holdings in *Capon* and *Invitrogen*, the present specification clearly provides a sufficient description of the presently claimed invention to meet the requirements of 35 U.S.C. § 112, first paragraph.

With regard to the Examiner's reliance on *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997), Applicants note that *Lockwood* does not require *in haec verba* support for claimed subject matter. Only an "equivalent description" is necessary, and whether or not a description is "equivalent" is viewed from the standpoint of a person of ordinary skill in the art reading the specification in context of knowledge in the art. *Id.* at 1572.

The Examiner also contends that: "[t]here is no disclosure of a polymer with hydrogen bonding sites capable of promoting release of the active compounds." Office Action, page 6, lines 9-10. Applicants respectfully submit that this contention has no relevance to the present claims. The presently claimed invention does not depend on "release" of the bioactive agent from the polyalkylene glycol moiety. In fact, the present specification discloses *covalent* bonding of a polyalkylene glycol moiety to the bioactive agent. *See* claims 1, 54, and Specification at pages 3-5, 11, 13, 17 and 24. Covalent

bonding of the polyalkylene glycol moiety to the bioactive reagent maximizes therapeutic efficacy as described in the presently claimed specification by increasing the serum half life of said bioactive reagent, and hence release of the bioactive reagent from the polyalkylene glycol moiety is neither required nor desired. *See* Specification at page 3, paragraph 5. In addition, the Examiner notes "[t]he specification is limited to the above mention[ed] cyclic molecules that share a common core." Office Action at page 6, lines 8-9. Applicants note that this also appears to have no relevance to the present claims, as nowhere is there any mention of cyclic molecules having a common core in the practice of the presently claimed invention.

The Examiner also cites *In re Wilder*, 736 F.2d 1516, 1521, for the contention that the present specification provides only an indication of a result that one might achieve if one made the invention. Office Action at page 6, lines 14-15. Applicants respectfully submit that the present specification clearly does more than simply outline the goals Applicants hope to achieve. In *Wilder*, Applicants simply set forth their desired goals in the Object of the Invention Section. 736 F.2d at 1521. In contrast, as noted above, the present specification clearly provides a full description of the presently claimed conjugates, including methods of preparing such conjugates, active agents that can be used in preparing such conjugates, as well as the conjugates themselves. Thus, the present specification clearly provides a sufficient written description of the presently claimed invention.

Hence, when viewed in light of the state of the art at the time of filing the present application, the ordinarily skilled artisan would readily recognize that the present specification fully supports the presently claimed invention, and that Applicants were in

full possession of the presently claimed invention at the time of filing. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are therefore respectfully requested.

Rejections under 35 U.S.C. § 112 First Paragraph, Enablement

In the Office Action at pages 6-10, the Examiner has rejected claims 1-11, 13-15, 17-27, 30, 35, 38, 59-67, 73-82, 85, 90, 93-96 and 101-108 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

The Examiner's reasoning for alleged lack of enablement appears to rest largely in part on (i) the chemical reactivity of the polyalkylene glycol reagent (*i.e.*, heterobifunctional or monofunctional) and (ii) the ability of the activated polyalkylene glycol reagent to conjugate with a single bioactive component without the formation of undesirable crosslinked reaction products as disclosed in Veronese, F.M., *et al.*, "Peptide and Protein PEGylation: a Review of Problems and Solutions," *Biomaterials 22*: 405-417 (2001) (hereinafter "Veronese") and Roberts, *et al.*, "Chemistry for Protein and Peptide PEGylation," *Advanced Drug Delivery Reviews 54:* 459-476 (2002) (hereinafter "Roberts"). Office Action at page 8, lines 1-7, page 8, lines 13-19, and the entirety of page 9. Specifically addressing the issue of crosslinking, the Examiner quotes Roberts with regard to the use of *heterobifunctional* PEGs in polymerization reactions under *non-aqueous* conditions (*i.e.*, ethoxylation). In particular:

> This [ethoxylation] strategy also has its limits. Only those anions that are desirable as end groups and suitable for initiating polymerization are useful for synthesis of *heterobifunctional* PEG by this route. This method

> is also limited by the fact that rigorous exclusion of water is necessary to prevent formation of the diol.

Office Action at page 8, lines 5-6.

The Examiner also states that:

> . . . the art recognizes that when PEG-diol is present, unwanted crosslinking occurs . . . . However, without protection of the free hydroxyl or how to prevent formation of [a] diol, a crosslinked product would occur.

Office Action, page 9, lines 18-23. The Examiner therefore concludes that the presently claimed invention is not enabled. Applicants respectfully disagree with these contentions and conclusions.

The portion of Roberts referred to by the Examiner in making this rejection discloses a chemical process of synthesizing and coupling PEG polymers under *non-aqueous* conditions (*i.e.*, ethoxylation). It appears to be the Examiner's contention that it would not be possible to generate the presently claimed conjugates due to the problems set forth above when utilizing non-aqueous conditions, and hence, the presently claimed invention is not enabled.

Applicants respectfully submit the present application does not utilize non-aqueous conditions, but rather discloses polyalkylene glycol (e.g., PEG) conjugation carried out under *aqueous* conditions. Therefore, the conditions the Examiner describes are not applicable to the conditions described and utilized in the present application. Under aqueous conditions, the terminal hydroxy group of the presently claimed polyalkylene glycol is chemically unreactive and the polyalkylene glycol molecules are *monofunctional* (i.e., a bioactive component attaches at a single site on the polyalkylene

glycol, with a distal hydroxyl terminus) with regard to substrate reactivity, not heterobifunctional as described in Roberts. The activated hydroxy-polyalkylene glycols of the presently claimed invention (e.g. PharmaPEG®) are monofunctionally active polymers that react with a bioactive agent under *aqueous* conditions as described in Examples 5 and 6 of the Specification. *See* Specification, page 59, paragraph 146, and page 62, paragraph 150, respectively. The resulting polymers are thus *monofunctionally* active from a biochemical standpoint. As monofunctional polyalkylene glycols are incapable of crosslinking to any significant degree, the issue of problematic diol formation and subsequent protein crosslinking raised by the Examiner is not relevant to the enablement of the presently claimed invention.

The Examiner continues this line of reasoning by stating that "[g]iven the state of art with respect [to] diol [formation] and crosslinking, it is highly unpredictable to form a PEG conjugate with one biological agent." Office Action, page 8, section (4). For the reasons described above, and well known to those of ordinary skill in the art, protein crosslinking cannot occur to any significant extent under the aqueous reaction conditions described in the present specification. Under the disclosed aqueous conditions, the monofunctional polymers that are produced can only react with one singular bioactive agent. Crosslinking cannot occur to any significant degree. Thus, the present specification clearly discloses methods for production of the presently claimed conjugates, specifically, conjugates with at least one bioactive component attached at a single site on the polyalkylene glycol, and hence, clearly meets the enablement requirement of 35 U.S.C. 112, first paragraph.

The Examiner further claims that:

> [t]he specification, however, does not provide any examples that demonstrate the coupling of a *heterobifunctional* PEG, with a free hydroxyl group, to a protein, especially GM-CSF. Such guidance is necessary because the art indicates that the strategy utilizing *heterobifunctional* PEG, that [has] a free hydroxyl group, also has limits.

Office Action, page 9, lines 11-14. Applicants respectfully submit that heterobifunctional polyalkylene glycol polymers are not an aspect of the presently claimed invention. As understood by one of ordinary skill in the art, the present claims are directed to *monofunctionally* active polyalkylene polymers (e.g., those that are readily conjugated to bioactive agents under *aqueous* conditions as described in the specification). Thus, the problematic issue of unwanted crosslinking cannot occur to any significant extent.

Regarding the Examiner's contention that the present specification does not provide sufficient enabling examples, Applicants note that Example 5, at page 59-61, provides a full procedure for producing monofunctional hydroxy-polyalkylene glycol molecules (e.g. PharmaPEG®). As set forth at pages 5-6, paragraph 0009, Applicants respectfully submit that the ordinarily skilled artisan would readily recognize that such polyalkylene glycol molecules could be readily coupled to various bioactive agents to form conjugates such as; PEG-GM-CSF, PEG-adenosine deaminase, PEG-superoxide dismutase (SOD), and PEG-urate oxidase. *See* Specification at page 5, paragraph 0009. Applicants note that the methods of forming such conjugates were well-known in the art, as taught in the incorporated references recited in paragraph 0009. Furthermore, the present specification at page 33-36 provides ample guidance with regard to specific

reaction conditions useful to conjugate polyalkylene glycol molecules to bioactive agents. Hence, preparations of the various conjugates of the presently claimed invention would not have required undue experimentation.

Applicants respectfully remind the Examiner that a specification is presumed to be enabling unless the Examiner provides acceptable objective evidence or sound scientific reasoning showing that it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention. *See In re Marzocchi*, 439 F.2d 220 (C.C.P.A. 1971). Moreover:

> [t]he purpose of [the enablement] provision is to assure that the inventor provides sufficient information about the claimed invention that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the patent specification and knowledge in the art.

Scripps Clinic & Research Foundation v. Genentech, Inc., 18 USPQ2d 1001, 1006 (Fed. Cir. 1991).

Furthermore, the proper standard of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the application, coupled with information known in the art, without undue experimentation. *See United States v. Telectronics, Inc.,* 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), citing *Hybritech, Inc. v. Monoclonal Antibodies, Inc.,* 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 107 S. Ct. 1606 (1987). In addition, the question of undue experimentation is a matter of degree, and "the key word is 'undue,' not 'experimentation.'" *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), quoting *In re Angstadt*, 190 USPQ 214, 219 (C.C.P.A. 1976). In order to enable a claimed invention, a specification need not teach, and preferably omits,

information that is well-known to those of ordinary skill in the art. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986); *Lindemann Maschinenfabrik v. American Hoist and Derrick*, 730 F.2d 1452, 1463 (Fed. Cir. 1984); *In re Wands*, 8 USPQ2d 1400, 1402 (Fed. Cir. 1988). In addition, one of ordinary skill in the art is deemed to know not only what is considered well-known, but also where to search for any needed starting materials. *See In re Howarth*, 210 USPQ 689, 692, (CCPA 1981).

As noted above, Applicants respectfully submit that the present specification clearly sets forth methods for the synthesis of polyalkylene glycol reagents, and methods for coupling the polyalkylene glycol molecules to bioactive components, including reaction conditions, temperatures, pHs, and amounts and concentrations of reagents. *See* Specification at pages 33-36. Moreover, as is clearly disclosed in the present application, suitable methods for polyalkylene glycol polymerization and protein conjugation were well known to those of ordinary skill in the art at the time of filing of the present application (*see* page 5, paragraph 0009). Applicants therefore submit that it would not have required undue experimentation to prepare the presently claimed hydroxy-polyalkylene glycol conjugates, including muteins, mimetics, variants, agonists, analogs and derivatives thereof, using the guidance provided in the present specification (*see supra*). One of ordinary skill in the art would have readily recognized that the methods set forth in the specification would result in the synthesis of monofunctionally active hydroxy-polyalkylene glycols capable of covalently reacting in a non-crosslinking manner with a wide variety of bioactive agents. While preparation of such conjugates may require some experimentation, a person of ordinary skill in the art would not

consider such experimentation to be undue, but rather routine. The experiments and conditions set forth in the present specification would be considered routine by a person of ordinary skill in the art, and would require only very straightforward, simple assays.

Furthermore, the test of whether an amount of experimentation is undue is not merely quantitative; a considerable amount of experimentation is permissible, if it is merely routine (*i.e.*, uses methods known to those of ordinary skill in the relevant arts), or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *See PPG Indus., Inc. v. Guardian Indus. Corp.,* 37 USPQ2d 1618, 1623 (Fed. Cir. 1996), citing *Ex parte Jackson*, 217 USPQ 804, 807 (Bd. Pat. App. Int. 1982). Hence, Applicants submit that preparation of hydroxy-polyalkylene glycol conjugates comprising a bioactive agent, would require only routine, and not undue, experimentation. Applicants respectfully assert that, using the guidance provided by the present specification, in view of information readily available in the art (*See e.g.,* page 5, paragraph 9), one of ordinary skill could easily make and use the presently claimed conjugates. Hence, under *Wright* and *Marzocchi*, and absent sufficient evidence to the contrary from the Examiner, Applicants respectfully submit that the presently claimed invention is fully enabled.

Therefore, in view of the teachings of the present specification and information that is known in the art (which, under *Hybritech*, *Lindemann Maschinenfabrik*, *Wands*, and *Howarth*, need not be taught in, and preferably is omitted from, the present specification), one of ordinary skill would be able to make and use the conjugates of the presently claimed invention with a reasonable expectation of success and without undue

experimentation. Accordingly, Applicants respectfully submit that the present specification fully enables the full scope of the presently claimed invention. Reconsideration and withdrawal of this portion of the rejection are therefore respectfully requested.

Rejections under 35 U.S.C. § 102(b)

In the Office Action at page 10, the Examiner has rejected Claims 1-11, 13-15, 17-27, 30, 35, 38, 94-95 under 35 U.S.C. § 102(b) as being allegedly anticipated by WO 95/34326, Kohno, *et al.* (hereinafter "Kohno"). Applicants respectfully traverse this rejection.

The Examiner contends that Kohno discloses the conjugation of TNF with PEG molecules. The Examiner alleges that since the PEG molecules were monosubstituted, and that since the starting material was PEG-α-β-bis-vinyl sulfone, the non-conjugated end of the PEG molecule would not contain an alkoxyl or aryloxyl group. The Examiner therefore concludes that the presently claimed invention is anticipated. Applicants respectfully disagree with the Examiner's contentions and conclusions.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 711 (Fed.Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). Applicants submit that Kohno does not disclose a linear or branched polyalkylene glycol conjugate which has a hydroxyl group at every distal terminus, as is recited in present claim 1. Thus, Kohno cannot and does not anticipate the presently claimed invention.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

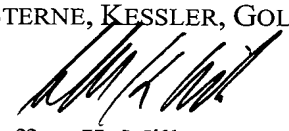
Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply are respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Jeffrey K. Mills
Attorney for Applicants
Registration No. 56,413

Date: November 20, 2007

1100 York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600
739261_5.DOC